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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 211/22, 211/14, 211/46
C07D 401/12, A61K 31/445

A1

(11) International Publication Number: WO 92/02502

(43) International Publication Date: 20 February 1992 (20.02.92)

(21) International Application Number: PCT/GB91/01340

(22) International Filing Date: 5 August 1991 (05.08.91)

(30) Priority data:
9017224.8 6 August 1990 (06.08.90) GB
9107757.8 12 April 1991 (12.04.91) GB

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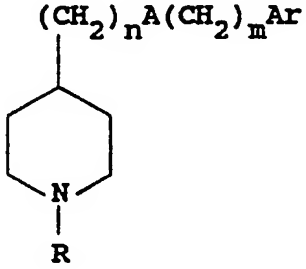
(81) Designated States: AT (European patent), AU, BB, BE (European patent), BG, BR, CA, CH (European patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, MW, NL (European patent), NO, PL, RO, + SD, SE (European patent), SU, US.

Published
With international search report.

(54) Title: N-HYDROCARBYL-4-SUBSTITUTED PIPERIDINES, THEIR PREPARATION AND USE AS CALCIUM BLOCKING AGENTS



(I)

(57) Abstract

Compounds of structure (I) in which R is C_{1-8}alkyl(phenyl)p, C_{2-8}alkenyl(phenyl)p, C_{2-8}alkenyl(phenyl)p, C_{3-8}cycloalkyl or C_{1-8}alkylC_{3-8}cycloalkyl; p is 0 to 2; n is 0 to 6; A is a bond, oxygen, sulphur or NR^1; R^1 is hydrogen, C_{1-8}alkyl or phenylC_{1-4}alkyl; m is 0 to 3; and Ar is aryl or heteroaryl, each of which may be optionally substituted, and salts thereof; processes for preparing said compounds, pharmaceutical compositions containing them and their use in therapy, in particular as calcium blocking agents.

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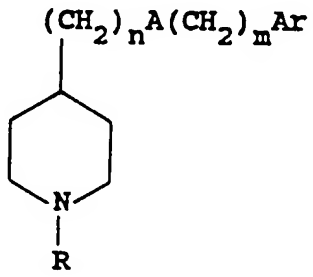
N-HYDROCARBYL-4-SUBSTITUTED PIPERIDINES, THEIR PREPARATION AND USE AS CALCIUM BLOCKING AGENTS

The present invention relates to 4-substituted piperidine derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

The present invention therefore provides, in a first aspect, compounds of structure (I):



(I)

in which

R is C_{1-8}alkyl(phenyl)p, C_{2-8}alkenyl(phenyl)p, C_{2-8}alkynyl(phenyl)p, C_{3-8}cycloalkyl or C_{1-8}alkylC_{3-8}cycloalkyl;

p is 0 to 2;

n is 0 to 6;

A is a bond, oxygen, sulphur or NR^1;

R^1 is hydrogen, C_{1-8}alkyl or phenylC_{1-4}alkyl;

m is 0 to 3; and

Ar is aryl or heteroaryl, each of which may be optionally substituted;

and salts thereof.

Suitably, R is C_{1-8}alkyl(phenyl)p, C_{2-8}alkenyl-(phenyl)p, C_{2-8}alkynyl(phenyl)p, C_{3-8}cycloalkyl or C_{1-8}alkylC_{3-8}cycloalkyl.

It will be understood that the alkylcycloalkyl, alkylphenyl, alkenylphenyl and alkynylphenyl groups are

linked to the piperidine nitrogen atom via the alkyl, alkenyl and alkynyl moieties respectively.

Preferably R is C_{1-8}alkyl(phenyl)p in which p is 0 or 1, i.e. C_{1-8}alkyl, such as n-pentyl, or phenylC_{1-8}alkyl such as phenylpropyl, or R is C_{2-8}alkenyl(phenyl)p where p is 1, such as cinnamyl.

Suitably, n is 0 to 6; preferably n is 0 to 3; most preferably n is 2 or 3.

Suitably, m is 0 to 3; preferably m is 0 or 1; most preferably m is 0.

Suitably, A is a bond, oxygen, sulphur or NR^1; preferably A is oxygen or sulphur; most preferably A is oxygen. When A is oxygen n is preferably 2 and m is preferably 0.

Suitably, Ar is optionally substituted aryl or heteroaryl; preferably Ar is optionally substituted aryl.

Suitable aryl groups include, for example, unsaturated monocyclic and unsaturated or partially saturated bicyclic ring systems of up to 10 carbon atoms, such as, for example, phenyl, naphthyl and tetrahydronaphthyl. Preferred are optionally substituted phenyl rings.

Suitable substituted phenyl rings include, for example, phenyl rings substituted by a C_{1-2}alkylene-dioxy group such as a 3,4-methylenedioxy group or by 1 to 3 substituents selected from halogen, C_{1-4}alkoxy, nitro, SC_{1-4}alkyl, NR^2R^2 (in which each R^2 group can be H or C_{1-4}alkyl), OCF_3, C_{1-6}alkyl,

trifluoromethyl, CN, optionally substituted phenyl, optionally substituted phenylC_{1-4}alkyl and optionally substituted phenylC_{1-4}alkoxy. Preferred are phenyl rings substituted by one or two substituents, in particular, by a single halogen, trifluoromethyl, unsubstituted phenyl or unsubstituted phenylC_{1-4}alkoxy group; or by two chlorine atoms, in particular in the 3 and 4 positions of the ring.

Suitable optionally substituted phenylC_{1-4}alkyl groups include, for example benzyl. Suitable optionally substituted phenylC_{1-4}alkoxy groups include, for example benzyloxy groups.

Suitable substituents for said optionally substituted phenyl, phenylC_{1-4}alkyl and phenylC_{1-4}alkoxy groups include for example halogen, C_{1-4}alkyl, C_{1-4}alkoxy, nitro and trifluoromethyl groups.

Suitable heteroaryl rings include, for example, unsaturated monocyclic and unsaturated or partially saturated bicyclic ring systems of up to 10 carbon atoms containing at least one heteroatom, such as pyridyl, thienyl, quinolinyl, tetrahydroquinolinyl and imidazolyl rings. The heteroaryl ring can be linked to the remainder of structure (I) via a carbon atom or via a hetero atom, e.g. a nitrogen atom.

Suitable substituents for said heteroaryl rings include, for example, 1 to 3 substituents selected from halogen, C_{1-4}alkyl and C_{1-4}alkoxy.

Alkyl groups present in the compounds of structure (I), alone or as part of another group, can be straight or branched.

It will be appreciated that for use in medicine a salt of a compound (I) should be pharmaceutically acceptable. Examples of pharmaceutically acceptable salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically acceptable inorganic or organic acid addition salts. Other non-pharmaceutically acceptable salts may be used for example as intermediates and are included within the scope of this invention.

Particular compounds of the invention include :

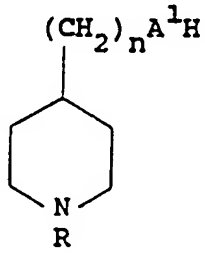
4-[2-(4-trifluoromethylphenoxy)ethyl]-1-pentylpiperidine oxalate,
4-[2-(3-trifluoromethylphenoxy)ethyl]-1-pentylpiperidine hydrochloride,
4-[2-(4-fluorophenoxy)ethyl]-1-pentylpiperidine hydrochloride,
4-[2-(3,4-methylenedioxyphenoxy)ethyl]-1-pentylpiperidine hydrochloride
4-(2-phenoxyethyl)-1-pentylpiperidine hydrochloride
4-[2-(4-phenylphenoxy)ethyl]-1-pentylpiperidine hydrochloride,
4-[2-(4-benzyloxyphenoxy)ethyl]-1-pentylpiperidine hydrochloride,
4-[2-(4-fluorophenoxy)ethyl]-1-cinnamylpiperidine oxalate,
4-(4-fluorobenzyloxy)-1-pentylpiperidine oxalate
4-[2-(3,4-dichlorophenoxy)ethyl]-1-pentylpiperidine hydrochloride,
4-[2-(4-benzylphenoxy)ethyl]-1-pentylpiperidine oxalate,
4-[2-(3,4-dichlorophenoxy)ethyl]-1-cinnamylpiperidine oxalate,
4-[2-(4-fluorophenoxy)ethyl]-1-(3-phenylpropylpiperidine hydrochloride,
4-[2-(4-fluorophenoxy)ethyl]-1-heptylpiperidine hydrochloride,
1-(3,3-diphenylpropyl)-4-[2-(4-fluorophenoxy)ethyl]-piperidine oxalate,

4-[2-(3,4-dichlorothiophenoxy)ethyl]-1-pentylpiperidine hydrochloride,
4-[2-(4-tert-butylphenoxy)ethyl]-1-pentylpiperidine hydrochloride,
4-[2-(4-iso-propylphenoxy)ethyl]-1-pentylpiperidine hydrochloride,
4-[2-(3,4-dichlorophenoxy)ethyl]-1-(3-phenylpropyl)-piperidine hydrochloride, and
1-cyclopropylmethyl-4-[2-(4-fluorophenoxy)ethyl]-piperidine oxalate.

It will be appreciated that the compounds of structure (I) may contain one or more asymmetric centres. Such compounds will exist as optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are included within the scope of the invention. Further, all diastereomeric forms possible (pure enantiomers and mixtures thereof) are within the scope of the invention.

The compounds of the present invention can be prepared by processes analogous to those known in the art. The present invention therefore provides in a further aspect, a process for the preparation of a compound of structure (I) which comprises:

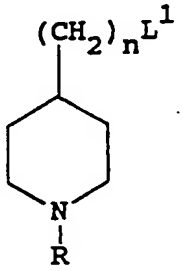
(a) for compounds of structure (I) in which A is O, S or NR^1, reaction of a compound of structure (II):



(II)

in which R and n are as described for structure (I) and A^1 is O, S or NR^1, with a compound of structure $L(CH_2)_mAr$ in which m and Ar are as described for structure (I), and L is a leaving group;

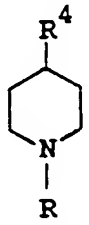
(b) for compounds of structure (I) in which A is O, S or NR^1, reaction of a compound of structure (III):



(III)

in which n and R are as described for structure (I) and L^1 is a group displaceable by a nucleophile, with a compound of structure $HA^1(CH_2)_mAr$ where m and Ar are as described for structure (I) and A^1 is as described for structure (II); or

(c) for compounds of structure (I) in which A is NR^1, reduction of a compound of structure (IV) :

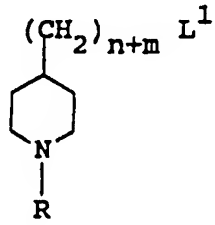


(IV)

in which R^4 represents the group

$-(CH_2)_nN(R^1)\overset{O}{\overset{\|}{C}}(CH_2)_{m-1}Ar$ or $-(CH_2)_{n-1}\overset{O}{\overset{\|}{C}}N(R^1)(CH_2)_mAr$, and n, m, R and Ar are as described for structure (I);

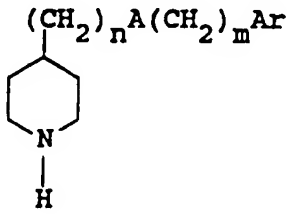
(d) for compounds of structure (I) in which A is a bond, reaction of a compound of structure (V) :



(V)

(wherein R, L^1, n and m are as hereinbefore defined) with a compound of structure X^1Ar in which Ar is as described for structure (I), and X^1 is an alkali metal;

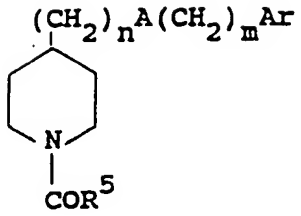
(e) introduction of the group R into a compound of formula (VI) :



(VI)

by reaction with a compound RL^2, wherein L^2 is a leaving group;

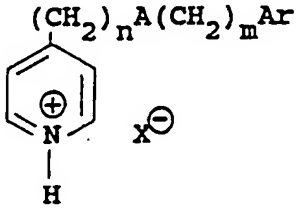
(f) Reduction of a compound of formula (VII) :



(VII)

wherein R^5 is C_{1-7}alkyl(phenyl)p, C_{2-7}alkenyl(phenyl)p, C_{2-7}alkynyl(phenyl)p or C_{1-7}alkylC_{3-8}cycloalkyl;

(g) Reduction of a compound of structure (VIII):



(VIII)

wherein R, A, Ar m and n are as hereinbefore defined and $X^{\ominus}$ is a counter ion;

and optionally thereafter forming a salt.

In process (a) the reaction between a compound of structure (II) and a compound $L(CH_2)_mAr$ can take place under conditions which depend on the nature of the group L. For example, when L is halogen or a sulphonic acid residue such as a tosylate or mesylate, the reaction is carried out under standard conditions in a solvent, optionally in the presence of a base. When a fluoro-substituted aryl F-Ar is employed in process (a), the reaction is effected in the presence of a strong base

such as sodium hydride, and in an inert organic solvent such as dimethyl formamide. Preferably the aryl group is substituted by an activating group such as CF_3 or NO_2.

The reaction between a compound of structure (III) and a compound of structure $HA^1(CH_2)_mAr$ can take place under conditions which depend on the nature of L^1 and A. For example when L^1 is hydroxy, m is 0 and A^1 is oxygen or sulphur, the reaction is carried out in the presence of diethyl azodicarboxylate and triphenyl phosphine. Such a reaction is known as the Mitsunobu reaction (as described in Synthesis 1981, 1). Alternatively the leaving group L^1 may be for example a halogen atom or a sulphonyloxy group eg. methanesulphonyloxy or p-toluenesulphonyloxy. In this case the reaction may be effected in the presence or absence of solvent at a temperature in the range 0 to 200°C

The reduction of a compound of structure (IV) can be effected by methods known in the art, for example using a reducing agent such as lithium aluminium hydride. Conveniently a compound of structure (IV) can be prepared (for example as described below) and reduced in a 'one-pot' reaction, without isolation of compound (IV) itself.

The reaction between a compound of structure (V) and a compound of structure X^1Ar can take place under standard conditions known to those skilled in the art for the formation of carbon-carbon bonds.

The reaction of a compound of structure (VI) with RL^2 according to process (e) may be effected in conventional manner, for example in an organic solvent, such as dimethyl formamide. The leaving group L^2 may be for example a halide such as bromide or chloride, an acyloxy group such as acetoxy or chloroacetoxy or a sulphonyloxy group such as methanesulphonyloxy or

p-toluene sulphonyloxy. When L^2 is a halide the reaction is preferably carried out in the presence of a weak base such as potassium carbonate, and when L^2 is sulphonyloxy, a strong base such as sodium hydride or potassium t-butoxide may be employed.

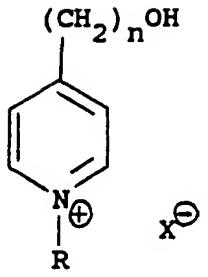
Reduction of a compound of formula (VII) may be effected using standard reducing agents such as lithium aluminium hydride.

Reduction of a compound of formula (VIII) may be effected for example by hydrogenation, using a noble metal catalyst such as platinum, palladium or platinum oxide, suitably in a solvent such as an alcohol eg. ethanol.

The compounds of structure (II) can be prepared from the corresponding compounds in which R is hydrogen, by alkylation under standard conditions. For example, compounds of structure (II) in which R is n-pentyl can be prepared from the corresponding precursor in which R is hydrogen by reaction with an n-pentylhalide such as n-pentyl bromide in a suitable solvent, such as methyl ethyl ketone, or a C_{1-4}alkanol such as ethanol, in the presence of a base, such as potassium carbonate, or dimethylformamide in the presence of an iodoalkane.

The corresponding compounds of structure (II) in which R is hydrogen are available commercially, known in the literature or can be prepared by standard techniques; for example by reduction of the corresponding 4-hydroxy-alkylpyridine.

Alternatively, compounds of structure (II) in which A^1 is oxygen can be prepared by reduction of a compound of structure (IX):



(IX)

in which R and n are as described for structure (I) and X^- is a counter ion.

Compounds of structure (III) wherein L^1 is OH can be prepared as described for compounds of structure (II), and compounds of structure (III) wherein L^1 is a halogen atom, or a mesyloxy or tosyloxy group can be prepared from the corresponding alcohol in conventional manner.

Compounds of structure (IV) wherein R^4 is a group $-(CH_2)_nN(R^1)\overset{O}{\overset{\|}{C}}(CH_2)_{m-1}Ar$ can be prepared by reacting a compound of structure (II) wherein A^1 represents NR^1 with an acylating agent corresponding to the group $-(CH_2)_mAr$, for example an acid chloride $ClOC(CH_2)_{m-1}Ar$.

Compounds of structure (IV) wherein R^4 is a group $-(CH_2)_{n-1}\overset{O}{\overset{\|}{C}}N(R^1)(CH_2)_mAr$ may be prepared for example by reaction of a corresponding compound wherein R^4 represents $-(CH_2)_{n-1}CO_2H$ or an activated derivative thereof such as an acid halide, ester or anhydride, with an amine of formula $HN(R^1)(CH_2)_m$ Ar. It will be appreciated that when the acid itself is employed, reaction with the amine should be effected in

the presence of a coupling agent. The carboxylic acid may itself be prepared for example by oxidation of the corresponding alcohol, ie. a compound of structure (II) wherein A^1 is oxygen.

Compounds of structure (V) may be prepared in analogous manner to compounds of structure (III); where necessary the chain length may be increased using methods well known in the art.

Compounds of structure (VI) may be prepared for example according to any of processes (a) to (d) above, using intermediates analogous to structures (II) to (IV) wherein R is replaced by an N-protecting group, which is subsequently removed by methods well known in the art. Suitable protecting groups include aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl and acyl groups such as acetyl, trifluoroacetyl, benzoyl, methoxycarbonyl, ethoxycarbonyl, or benzyloxycarbonyl. An aralkyl group such as benzyl may be cleaved by hydrogenolysis, and an acyl group such as benzoyl may be cleaved by hydrolysis. It will be appreciated that where the N-protecting group is aralkyl, the compound is of structure (I) and this reaction sequence thus provides a means of converting one compound of formula (I) into a different compound of formula (I).

A compound of formula (VII) may be prepared by reaction of a compound of formula (VI) with an appropriate acid derivative for example an acid chloride, or anhydride.

A compound of structure (VIII) may be prepared using the general methods described in processes (a) to (e) above. In addition compounds of structure (VIII) wherein A represents a bond may be prepared from 4-methyl

pyridine (picoline) by reaction with a compound of formula $L(CH_2)q\ Ar$ wherein L and Ar are as hereinbefore defined and q is (m+n-1), in the presence of a strong base such as sodium amide in liquid ammonia or an alkyl lithium. The resulting substituted pyridine is then reacted with a compound RL^2, as hereinbefore defined, to give a quaternary pyridinium compound of formula (VIII). Reduction of this compound according to process (g) provides a convenient method of preparing compounds of structure (I) wherein A represents a bond.

The compounds of the invention have been found to exhibit high calcium influx blocking activity and as such are expected to be of use in therapy in treating conditions and diseases related to an accumulation of calcium in the brain cells of mammals, in particular humans. For example, the compounds are expected to be of use in the treatment of anoxia, ischaemia including for example stroke, migraine, epilepsy, traumatic head injury, AIDS-related dementia, neurodegenerative diseases such as Alzheimer's disease and age-related memory disorders, and drug addiction withdrawal such as ethanol addiction withdrawal.

In a further aspect of the invention there is therefore provided a method of treatment of conditions or diseases caused or exacerbated by the accumulation of calcium in the brain cells of mammals which comprises administering to a subject in need thereof an effective amount of a compound of structure (I) or a pharmaceutically acceptable salt thereof. In addition, the present invention also provides a method of treatment of anoxia, ischaemia including for example stroke, migraine, epilepsy, traumatic head injury, AIDS-related dementia, neurodegenerative diseases such as Alzheimer's disease and age-related memory disorders, and drug addiction withdrawal such as ethanol addiction

withdrawal, which comprises administering to a subject in need thereof, an effective amount of a compound of structure (I) or a pharmaceutically acceptable salt thereof. The invention also provides the use of a compound of structure (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of the aforementioned conditions or diseases.

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of structure (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Compounds of the invention may also be administered parenterally, by bolus injection or continuous infusion. Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptabl salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 60 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, eg. 5 to 200 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 60 mg, eg. 1 to 40 mg of the compound of the formula (I)

or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Alternatively the compounds of the invention may be administered by continuous intravenous infusion, preferably at a dose of up to 100mg per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

DATA

Ca^{2+} Current Measurement

Cell preparations

Sensory neurons from dorsal root ganglia were dissociated from 1 day old rat pups (Forda et al, Developmental Brain Research, 22 (1985), 55-65). Cells were plated out onto glass coverslips and used within 3 days to permit effective voltage clamp of Ca^{2+} currents.

Solutions

The pipette (internal solution) contained in mM: CsCl, 130; HEPES, 10; EGTA, 10; $MgCl_2$, 4; ATP, 2; buffered to pH 7.2 with CsOH.

Cells were bathed in a normal Tyrodes solution before establishment of whole cell recording when the bathing solution was changed to one allowing isolation of Ca^{2+} currents.

The external solution for recording Ca^{2+} channel currents contained in mM: $BaCl_2$, 10; TEA-Cl, 130; glucose, 10; HEPES, 10; $MgCl_2$, 1; buffered to pH 7.3 with TEA-OH. Barium was used as the charge carrier as this assists in current isolation and calcium dependent inactivation of current is avoided.

Compounds were dissolved in DMSO to make a 20 mM stock solution. At the drug concentration used the vehicle (0.1%) had no significant effect on Ca^{2+} currents.

All experiments were performed at 21 to 24°C. Whole cell currents were recorded using List EPC-7 amplifiers and stored, digitised for later analysis using

PC based software similar to that described previously (Benham & Tsien, Journal of Physiology (1988), 404, 767-784).

RESULTS

Ca^{2+} currents

Peak voltage gated Ca^{2+} channel currents of up to 10 nA from dorsal root ganglion neurons were recorded using 10 mM Ba^{2+} as charge carrier. Currents were evoked from a holding potential of -80 mV to a test potential of 0 or +10 mV every 15 seconds. This test potential was at the peak of the current voltage relationship and assessing block at this point reduced any errors due to drifting holding potential. Some cells showed slow rundown of current as is commonly seen when recording Ca^{2+} currents. The rundown rate was measured in control conditions and extrapolated through the time of drug application to derive a control value to relate the drug affected current to. Block by 20 μM drug was assessed 3 minutes after drug application.

Compounds of the invention gave percentage inhibition of plateau Ca^{2+} current in the range 30 to 100%

TOXICOLOGY

The compound of Example 9 did not show any adverse toxicological effects when administered to rats at a dose of 10 mg/kg, i.v.

PHARMACEUTICAL FORMULATIONS

1. Formulation for intravenous infusion

Compound of structure (I)	0.1 - 60 mg
Sodium hydroxide/hydrochloric acid	to pH ca 7
polyethylene glycol	0 - 30 ml
propylene glycol	0 - 30 ml
alcohol	0 - 10 ml
water	to 100 ml

2. Formulation for bolus injection

Compound of structure (I)	0.1 - 60 mg
sodium hydroxide or hydrochloric acid	to pH ca 7
polyethylene glycol	0 - 2.5 ml
alcohol	0 - 2.5 ml
water	to 5 ml

A toxicity adjusting agent eg. sodium chloride, dextrose or mannitol may also be added.

3. Tablet for oral administration

	mg/tablet
Compound of structure (I)	25
lactose	153
starch	33
crospovidone	12
microcrystalline cellulose	30
magnesium stearate	2
	255

EXAMPLES

Intermediate Preparations

(i) 4-(2-Hydroxyethyl)-1-pentylpiperidine

A mixture of 4-(2-hydroxyethyl)piperidine (20g), 1-bromopentane (19.2g), potassium carbonate (21.42g) and ethanol (400ml) was heated at reflux for 3 days. The solution was filtered, and the solvent was removed under reduced pressure. The residue was treated with acetone, filtered, and the solvent was removed to give the title compound as an oil (30.2g) which was used without further purification.

(ii) 4-(2-Hydroxyethyl)-1-cinnamylpiperidine

A mixture of 4-(2-hydroxyethyl)piperidine (16.4g), cinnamyl bromide (25.0g), potassium carbonate (17.55g) and ethanol (350ml) was heated at reflux for 3 days. The solution was filtered, and the solvent removed under reduced pressure. The residue was chromatographed on silica gel eluted with methanol/dichloromethane to give the title compound (12.0g) as an inpure solid which was used without further purification.

(iii) 4-(3-Hydroxypropyl)-1-pentylpyridinium bromide

A solution of 4-(3-hydroxypropyl)pyridine (27.43g), 1-bromopentane (37.76g) and acetone (50ml) was refluxed for 24 hours, cooled and poured into diethylether (200ml). The oil which precipitated was collected by decantation then washed by decantation with diethylether (5 X 100ml) and dried at 50°C 0.1mmHg to give the title compound which was used without further purification.

(iv) 4-(3-Hydroxypropyl)-1-pentylpiperidine

A mixture of 4-(3-hydroxypropyl)-1-pentylpyridinium bromide (8.65g), platinum oxide (0.5g) and ethanol (120ml) was stirred under an atmosphere of hydrogen for 3 hours. The mixture was filtered and the solvent removed. The residue was dissolved in dilute sodium hydroxide (70ml) and extracted with dichloromethane (3 x 75ml). The extracts were combined, dried over magnesium sulphate and the solvent was removed to give the title compound as an oil (4.68g).

v) 4-Hydroxymethyl-1-pentylpyridinium bromide

A solution of 4-hydroxymethylpyridine (25g), 1-bromopentane (43.2g) and acetone (50ml) was refluxed for 24 hours, cooled and poured into diethylether (200ml). The oil which precipitated was collected by decantation then washed by decantation with pentane (5 X 100ml) and dried at 50°C 0.1mmHg to give the title compound which was used without further purification.

(vi) 4-Hydroxymethyl-1-pentylpiperidine

A mixture of 4-(3-hydroxypropyl)-1-pentylpyridinium bromide (5.2g), platinum oxide (0.4g) and ethanol (100ml) was stirred under an atmosphere of hydrogen for 3 hours. The mixture was filtered and the solvent removed. The residue was dissolved in dilute sodium hydroxide (70ml) and extracted with dichloromethane (3 x 75ml). The extracts were combined, dried over magnesium sulphate and the solvent was removed. The residue was chromatographed on silica gel eluted with methanol/ammonia/dichloromethane to give the title compound as an oil (1.35g).

(vii) 4-Hydroxy-1-pentylpiperidine

A mixture of 4-hydroxypiperidine (25g), 1-bromopentane (37.33g), potassium carbonate (34.13g) and ethanol (400ml) was heated at reflux for 3 days. The solution was filtered, and the solvent removed under reduced pressure. The residue was treated with acetone, filtered, the solvent removed and the resulting oil distilled under reduced pressure to give the title compound as an oil. (18.00g, b.p. 100 °C @ 0.6 mmHg.)

(viii) 4-(2-Hydroxyethyl)-1-propylpiperidine

A mixture of 4-(2-hydroxyethyl)piperidine (5g), 1-bromopropane (4.87g), potassium carbonate (5.5g) and ethanol (100ml) was heated at reflux for 1 day. The solution was filtered, and the solvent was removed under reduced pressure. The residue was treated with acetone, filtered, and the solvent was removed to give the title

compound as an oil (5.1g) which was used without further purification.

(ix) 4-(2-Hydroxyethyl)-1-(3-phenyl)propylpiperidine

A mixture of 4-(2-hydroxyethyl)piperidine (10g), 1-bromo-3-(phenyl)propane (15.8g), potassium carbonate (10.69g) and ethanol (200ml) was heated at reflux for 24 hours. The solution was filtered, and the solvent was removed under reduced pressure. The residue was treated with acetone, filtered, the solvent removed and the residue distilled, to give the title compound as an oil (14.52g) (b.p. 141°C @ 0.2mmHg)

(x) 4-(2-Hydroxyethyl)-1-heptylpiperidine

A mixture of 4-(2-hydroxyethyl)piperidine (20g), 1-bromoheptane (27.73g), potassium carbonate (21.39g) and ethanol (400ml) was heated at reflux for 24 hours. The solution was filtered, and the solvent was removed under reduced pressure. The residue was treated with acetone, filtered, the solvent was removed and the residue distilled, to give the title compound as an oil (10.01g) (b.p. 110°C @ 0.1mmHg)

(xi) 4-(2-Hydroxyethyl)-1-(2-ethyl)butylpiperidine

A mixture of 4-(2-hydroxyethyl)piperidine (20g), 1-bromo-2-ethylbutane (17.9g), potassium carbonate (26g) and ethanol (400ml) was heated at reflux for 4 days. The solution was filtered, and the solvent was removed under

reduced pressure. The residue was distilled, to give the title compound as an oil (29.61g) (b.p. 102°C @ 0.3mmHg)

(xii) 1-Cyclohexylmethyl-4-(2-hydroxyethyl)piperidine

A mixture of 4-(2-hydroxyethyl)piperidine (20g), cyclohexylmethyl bromide (27.41g), potassium carbonate (26g) and ethanol (400ml) was heated at reflux for 4 days. The solution was filtered, and the solvent was removed under reduced pressure. The residue was distilled, to give the title compound as an oil (27g) (b.p. 165°C @ 0.5mmHg)

(xiii) 4-(2-hydroxyethyl)-1-(3-methylbutyl)piperidine

A mixture of 4-(2-hydroxyethyl)piperidine (20g), 1-bromo-3-methylbutane (25.57g), potassium carbonate (26g) and ethanol (400ml) was heated at reflux for 4 days. The solution was filtered, and the solvent was removed under reduced pressure. The residue was distilled to give the title compound as an oil (23.21g) (b.p. 98°C @ 0.1mmHg)

(xiv) 1-Benzyl-4-(2-hydroxyethyl)piperidine

A mixture of 4-(2-hydroxyethyl)piperidine (5g), benzyl bromide (6.15g), potassium carbonate (5.35g) and ethanol (50ml) was heated at reflux for 24 hours. The mixture was poured into water (200ml) and extracted with diethylether. The organic phase was dried over sodium sulphate, filtered, and the solvent was removed under reduced pressure. The residue was distilled, to give the title compound as an oil (5.13g) (b.p. 120-130°C @ 0.1mmHg)

(xv) 4-[2-(4-Fluorophenyl)ethyl]-pyridine

4-Picoline (30g) was added over 30 minutes to a suspension of sodium amide (12.56g) in liquid ammonia (150ml) and the resulting mixture was stirred for 1.5 hours. 4-Fluorobenzyl chloride (40ml) was then added over 15 minutes and the mixture was stirred for 3-hours. Ammonium chloride (50g) was added and the solvent was allowed to evaporate. The residue was dissolved in chloroform (300ml) and dilute sodium hydroxide (300ml) and the organic phase was separated, dried over magnesium sulphate and the solvent was removed. The residue was recrystallised from petroleum ether to give the title compound as white needles (25.3g), m.p. 69-70.5°C

(xvi) 4-[2-(4-Fluorophenyl)ethyl]-1-pentylpyridinium bromide

A mixture of 4-[2-(4-fluorophenyl)ethyl)pyridine (5g), 1-bromopentane (7.0g) and acetone (10ml) was heated at reflux for 18 hours. The solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate / methanol to give the title compound (7.32g), m.p. 130 - 131°C.

(xvii) 4-[2-(4-Fluorophenoxy)ethyl]-piperidine hydrochloride

A mixture of 1-benzyl-4-[2-(4-fluorophenoxy)ethyl]piperidine (1.50g), 10% palladium on carbon (0.6g) and ethanol (120ml) was shaken under an

atmosphere of hydrogen at 50 p.s.i for 24 hours. The mixture was filtered and the residue washed with ethanol. The filtrates were combined, the solvent removed and the residue was treated with hydrogen chloride in ether to give a solid. Recrystallisation from ethyl acetate gave the title compound (0.45g), m.p. 122 -123°C.

Found: C, 59.58; H, 7.37; N, 5.35; Cl, 13.33%
($C_{13}H_{18}FNO.HCl$) requires: C, 60.11; H, 7.37; N, 5.39; Cl, 13.65%

Example 1

4-[2-(4-Fluorophenoxy)ethyl]-1-pentylpiperidine hydrochloride

A solution of 4-(2-hydroxyethyl)-1-pentylpiperidine (2.0g), 4-fluorophenol (1.12g) and triphenylphosphine (2.62g) in tetrahydrofuran (40ml) was treated with diethyl azodicarboxylate (1.74g) in tetrahydrofuran (10ml). The resulting solution was stirred at room temperature for 18 hours, the solvent was removed and the residue was chromatographed on silica gel eluted with methanol/dichloromethane. The resulting oil was dissolved in ethyl acetate (50ml) and treated with ethereal hydrogen chloride, the precipitate was collected by filtration and recrystallised (methanol/ethyl acetate) to give the title compound (1.1g), m.p. 167-169 °C.

Found: C, 65.45; H, 8.90; N, 4.16; Cl, 10.75; F 5.76%.
($C_{18}H_{28}FNO.HCl$) requires: C, 65.54; H, 8.86; N, 4.25; Cl, 10.75; F, 5.77%.

Example 2

4-[2-(3,4-Methylenedioxyphenoxy)ethyl]-1-pentylpiperidine hydrochloride

A solution of 4-(2-hydroxyethyl)-1-pentylpiperidine (2.0g), sesamol (1.39g) and triphenylphosphine (2.62g) in tetrahydrofuran (40ml) was treated with diethyl azodicarboxylate (1.74g) in tetrahydrofuran (10ml). The resulting solution was stirred at room temperature for 18 hours, the solvent was removed and the residue was chromatographed on silica gel eluted with methanol/dichloromethane. The resulting oil was dissolved in ethyl acetate (50ml) and treated with ethereal hydrogen chloride. The precipitate was collected by filtration and recrystallised (methanol/ethyl acetate) to give the title compound (0.45g), m.p. 134 - 136°C.

Found: C, 64.12; H, 8.52; N, 4.03; Cl, 10.00%. ($C_{19}H_{29}NO_3$.HCl) requires: C, 64.12; H, 8.50; N, 3.93; Cl, 9.96%.

Example 3

4-(2-Phenoxyethyl)-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (2.0g), phenol (0.94g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was

recrystallised from methanol/ethyl acetate (0.88g), m.p. 158 - 159°C.

Found: C, 69.10; H, 9.80; N, 4.61; Cl, 11.34%
($C_{18}H_{29}NO.HCl$) requires: C, 69.32; H, 9.69; N, 4.49; Cl, 11.37%

Example 4

4-[2-(3-Trifluoromethylphenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (2.0g), α,α,α, trifluoro-m-cresol (1.62g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from methanol/ethyl acetate (0.44g), m.p. 154°C.

Found: C, 59.51; H, 7.62; N, 3.80; Cl, 9.49%
($C_{19}H_{28}F_3NO.HCl$) requires: C, 60.07; H, 7.69; N, 3.69; Cl, 9.33%

Example 5

4-[2-(4-Phenylphenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (2.0g), 4-phenylphenol (0.1.70g), triphenylphosphine

(2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from methanol/ethyl acetate (0.4g), m.p. 205-206°C.

Found: C,73.77 ; H, 8.88; N, 3.66; Cl, 9.14%
($C_{24}H_{33}NO.HCl$) requires: C, 74.2; H, 8.8; N, 3.6; Cl, 9.27%

Example 6

4-[2-(4-Benzyloxyphenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (1.0g), 4-benzyloxyphenol (1.00g), triphenylphosphine (1.31g) and diethyl azodicarboxylate (0,87g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from methanol/ethyl acetate (0.1g), m.p. 168 - 169°C.

Found: C, 70.42; H, 8.59; N, 3.50; Cl, 8.29%
($C_{25}H_{35}NO_2.HCl.0.5H_2O$) requires: C, 70.31; H, 8.73; N, 3.28; Cl, 8.20%

Example 7

4-[2-(3-Dimethylaminophenoxy)ethyl]-1-pentylpiperidine dioxalate

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (2.2g), 3-dimethylaminophenol (1.5g), triphenylphosphine (2.88g) and diethyl azodicarboxylate (1.94g). Treating the product with oxalic acid gave a white solid which was recrystallised from methanol/ethyl acetate (0.2g), m.p. 128-130°C.

Found: C, 57.82; H, 7.63; N, 5.62%
($C_{20}H_{34}N_2O.2C_2H_2O_4$) requires: C, 57.83; H, 7.63; N, 5.62%

Example 8

4-[2-(4-Methoxyphenoxy)ethyl]-1-pentylpiperidine oxalate

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (1.5g), 4-methoxyphenol (0.93g), triphenylphosphine (1.97g) and diethyl azodicarboxylate (1.31g). Treating the product with oxalic acid gave a white solid which was recrystallised from methanol/ethyl acetate (0.53g), m.p. 119-121°C.

Found: C, 63.54; H, 8.47; N, 3.69%
($C_{19}H_{31}NO_2.C_2H_2O_4$) requires: C, 63.79; H, 8.35; N, 3.54%

Example 9

4-[2-(3,4-Dichlorophenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (2.0g), 3,4-dichlorophenol (1.63g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.76g). Treating the product with hydrogen chloride gave the title compound as white prisms from methanol/ethyl acetate (1.02g), m.p. 177 - 178°C.

Found: C, 57.05; H, 7.43; N, 3.85; Cl, 27.93%
($C_{18}H_{27}Cl_2NO.HCl$) requires: C, 56.78; H, 7.41; N, 3.68; Cl, 27.93%

Example 10

4-[2-(4-Cyanophenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (2.0g), 4-cyanophenol (1.19g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from methanol/ethyl acetate (0.95g), m.p. 173 - 174°C.

Found: C, 67.69; H, 8.84; N, 8.28; Cl, 10.85%
($C_{19}H_{28}N_2O.HCl$) requires: C, 67.74; H, 8.68; N, 8.31; Cl, 10.52%

Example 11

4-[2-(4-Chlorophenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (2.0g), 4-chlorophenol (1.30g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from methanol/ethyl acetate (0.75g), m.p. 185 -186°C.

Found: C, 62.14; H, 8.48; N, 4.44; Cl, 20.63%
($C_{18}H_{28}ClNO.HCl$) requires: C, 62.42; H, 8.44; N, 4.04; Cl, 20.47%

Example 12

4-[2-(5,6,7,8-Tetrahydro-2-napthoxy)ethyl]-1-pentylpiperidine oxalate

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (2.0g), 5,6,7,8-tetrahydro-2-napthol (1.48g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with oxalic acid gave a white solid which was recrystallised from methanol/ethyl acetate (0.81g), m.p. 147°C.

Found: C, 68.88; H, 9.07; N, 3.40%
($C_{22}H_{35}NO.C_2H_2O_4$) requires: C, 68.71; H, 8.89; N, 3.34%

Example 13

4-[2-(5,6,7,8-Tetrahydro-1-napthoxy)ethyl]-1-pentylpiperidine oxalate

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (2.0g), 5,6,7,8-tetrahydro-1-napthol (1.48g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with oxalic acid gave a white solid which was recrystallised from methanol/ethyl acetate (1.14g), m.p. 162°C.

Found: C, 68.03; H, 8.73; N, 3.40%
($C_{22}H_{35}NO.C_2H_2O_4.0.25H_2O$) requires: C, 67.97; H, 8.84; N, 3.30%

Example 14

4-[2-(4-Nitro-3-trifluoromethylphenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (1.5g), 3-nitro-4-trifluoromethylphenol (1.44g), triphenylphosphine (1.96g) and diethyl azodicarboxylate (1.19g). Treating the product with hydrogen chloride gave the title compound as a white solid from methanol/ethyl acetate (0.61g), m.p. 139 - 141°C.

Found: C, 53.80; H, 6.50; N, 6.45; Cl, 8.30%

($C_{19}H_{27}F_3N_2O_3$.HCl) requires: C, 53.71; H, 6.64; N, 6.59; Cl, 8.34%

Example 15

4-[2-(3-Fluorophenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (1.5g), 3-fluorophenol (0.84g), triphenylphosphine (1.97g) and diethyl azodicarboxylate (1.31g). Treating the product with hydrogen chloride gave the title compound as a white solid from methanol/ethyl acetate (1.21g), m.p. 157-159°C.

Found: C, 65.27; H, 8.67; N, 4.61; Cl, 10.75%
($C_{18}H_{28}FNO$.HCl) requires: C, 65.54; H, 8.86; N, 4.25; Cl, 10.75%

Example 16

4-[2-(4-Methylphenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (1.50g), p-cresol (0.81g), triphenylphosphine (1.96g) and diethyl azodicarboxylate (1.31g). Treating the product with hydrogen chloride gave the title compound as a white solid from methanol/ethyl acetate (1.09g), m.p. 164 - 166°C.

Found: C, 70.00; H, 9.69; N, 4.15; Cl, 10.82%
($C_{19}H_{31}NO.HCl$) requires: C, 70.02; H, 9.90; N, 4.30; Cl, 10.88%

Example 17

4-[2-(4-Benzylphenoxy)ethyl]-1-pentylpiperidine oxalate

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (1.50g), 4-benzylphenol (1.38g), triphenylphosphine (1.96g) and diethyl azodicarboxylate (1.31g). Treating the product with oxalic acid gave the title compound as a white solid from methanol/ethyl acetate (0.377g), m.p. 166 - 168°C.

Found: C, 70.86; H, 8.02; N, 3.07%
($C_{25}H_{35}NO.C_2H_2O_4$) requires: C, 71.18; H, 8.19; N, 3.07%

Example 18

4-[2-(3-chlorophenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (1.50g), 3-chlorophenol (0.69g), triphenylphosphine (1.96g) and diethyl azodicarboxylate (1.31g). Treating the product with hydrogen chloride gave the title compound as a white solid from methanol/ethyl acetate (0.37g), m.p. 151 - 153°C.

Found: C, 62.13; H, 8.30; N, 4.05; Cl^-, 10.20%
($C_{18}H28ClNO.HCl$) requires: C, 62.42; H, 8.44; N, 4.04; Cl^-, 10.23%

Example 19

4-Benzyl-1-pentylpiperidine hydrochloride

A mixture of 4-benzylpiperidine (3.0g), pentyl bromide (2.84g), potassium carbonate (4.72g) and ethanol (40ml) was heated at reflux for 48 hours. The solution was filtered, and the solvent removed under reduced pressure. The residue was distilled in a kugelrohr apparatusto give an oil (b.p. 150°C @ 0.1mmHg) which was treated with hydrogen chloride to gave the title compound as a white solid from methanol/ethyl acetate (2.06g), m.p. 188 - 190°C.

Found: C, 70.00; H, 9.69; N, 4.15; Cl, 10.82%
($C_{19}H_{31}NO.HCl$) requires: C, 70.02; H, 9.90; N, 4.30; Cl, 10.88%

Example 20

4-[2-(4-Fluorophenoxy)ethyl]-1-cinnamylpiperidine oxalate

A solution of 4-(2-hydroxyethyl)-1-cinnamylpiperidine (2.94g), 4-fluorophenol (1.31g) and triphenylphosphine (3.15g) in tetrahydrofuran (50ml) was treated with diethyl azodicarboxylate (2.09g). The resulting solution was stirred at room temperature for 18 hours, the solvent

removed and the residue chromatographed on silica gel eluted with methanol/dichloromethane. The resulting oil was dissolved in ethyl acetate (50ml) and treated with oxalic acid (1.1 mole equivalents). The precipitate was collected by filtration and recrystallised (methanol/ethyl acetate) to give the title compound (1.10g), m.p. 180 °C.

Found: C, 67.14; H, 6.60; N, 3.56%.
($C_{22}H_{26}FNO.C_2H_2O_4$) requires: C, 67.11; H, 6.57; N, 3.26%

Example 21

4-[2-(3,4-Dichlorophenoxy)ethyl]-1-cinnamylpiperidine oxalate

A solution of 4-(2-hydroxyethyl)-1-cinnamylpiperidine (2.02g), 3,4-dichlorophenol (1.34g) and triphenylphosphine (2.16g) in tetrahydrofuran (50ml) was treated with diethyl azodicarboxylate (1.44g). The resulting solution was stirred at room temperature for 18 hours, the solvent removed and the residue was dissolved in ethyl acetate and extracted with dilute hydrochloric acid. The aqueous extract was basified and extracted with ethyl acetate. The resulting organic layer was dried over magnesium sulphate, filtered and the solvent was removed. The residue was dissolved in ethyl acetate (50ml) and treated with oxalic acid (1.1 mole equivalents). The precipitate was collected by filtration and recrystallised (methanol/ethyl acetate) to give the title compound (0.3g), m.p. 179 - 180°C.

Found: C, 60.07; H, 5.67; N, 2.92; Cl, 14.79%.

($C_{22}H_{25}Cl_2NO.C_2H_2O_4$) requires: C, 60.01; H, 5.67; N, 2.92; Cl, 14.76%

Example 22

4-[3-(4-Fluorophenoxy)propyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 1-pentyl-4-(3-hydroxypropyl)piperidine (2.0g), 4-fluorophenol (1.05g), triphenylphosphine (2.46g) and diethyl azodicarboxylate (1.63g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from methanol/ethyl acetate (1.32g), m.p. 148 - 150°C.

Found: C, 65.94; H, 9.29; N, 4.15; Cl, 10.32%
($C_{19}H_{30}FNO.HCl$) requires: C, 66.36; H, 9.09; N, 4.07; Cl, 10.31%

Example 23

4-[3-(4-Benzyloxyphenoxy)propyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 1-pentyl-4-(3-hydroxypropyl)piperidine (2.0g), 4-benzyloxyphenol (1.88g), triphenylphosphine (2.46g) and diethyl azodicarboxylate (1.48g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from acetonitrile (1.48g), m.p. 163 - 164°C.

Found: C, 72.43; H, 8.91; N, 3.31; Cl, 8.06%
($C_{26}H_{37}NO_2$.HCl) requires: C, 72.28; H, 8.86; N, 3.24; Cl, 8.21%

Example 24

4-(4-Fluorophenoxy)methyl-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 1-pentyl-4-hydroxymethylpiperidine (1.1g), 4-fluorophenol (0.69g), triphenylphosphine (1.63g) and diethyl azodicarboxylate (1.08g). Treating the product with oxalic acid gave a white solid which was recrystallised from methanol/ethyl acetate (0.25g), m.p. 111 -112°C.

Found: C, 60.25; H, 7.56; N, 3.88%
($C_{17}H_{26}FNO.C_2H_2O_4.0.5H_2O$) requires: C, 60.3; H, 7.72; N, 3.70%

Example 25

4-(4-Fluorobenzyloxy)-1-pentylpiperidine oxalate

A solution of 4-hydroxy-1-pentylpiperidine (2.0g) in dimethylformamide (25 ml) was treated with sodium hydride (0.012 mole) and then stirred for 1 hour when 4-fluorobenzyl chloride (1.43 ml) was added and the mixture was stirred for 3 days. Water (100 ml) and dichloromethane (100 ml) were added and the organic layer was separated, washed with water (2 x 100 ml), and dried

over magnesium sulphate. The solvent removed and the residue was chromatographed on silica gel eluted with methanol/dichloromethane. The resulting oil was dissolved in ethyl acetate and treated with oxalic acid (1.1 mole equivalent). The precipitate was collected by filtration and recrystallised (methanol/ethyl acetate) to give the title compound (0.2g), m.p. 124 - 125 °C.

Found: C, 61.71; H, 7.69; N, 3.94%.
($C_{17}H_{26}FNO.C_2H_2O_4$) requires: C, 61.77; H, 7.64; N, 3.79%

Example 26

4-Benzyloxy-1-pentylpiperidine oxalate

Substitution of benzyl bromide (2.0g) for 4-fluorobenzyl chloride, in the procedure described in example 25, gave the title compound as a white solid on recrystallisation from methanol/ethyl acetate yield (0.2g), m.p. 119 - 121°C.

Found: C, 64.63; H, 8.11; N, 4.14%
($C_{17}H_{27}NO.C_2H_2O_4$) requires: C, 64.98; H, 8.32; N, 3.99%

Example 27

4-(4-Fluorophenoxy)-1-pentylpiperidine oxalate

The title compound was prepared in a similar manner to example 1 from 4-hydroxy-1-pentylpiperidine (2.0g), 4-fluorophenol (1.31g), triphenylphosphine (3.15g) and diethyl azodicarboxylate (2.09g). Treating the product

with oxalic acid gave a white solid which was recrystallised from methanol/ethyl acetate (0.65g), m.p. 164°C.

Found: C, 60.91; H, 7.56; N, 4.06%
($C_{16}H_{24}FNO.C_2H_2O_4$) requires: C, 60.83; H, 7.37; N, 3.94%

Example 28

4-(3,4-Methylenedioxyphenoxy)-1-pentylpiperidine oxalate

The title compound was prepared in a similar manner to example 1 from 4-hydroxy-1-pentylpiperidine (2.0g), sesamol (1.66g), triphenylphosphine (3.15g) and diethyl azodicarboxylate (2.09g). Treating the product with oxalic acid gave a white solid which was recrystallised from methanol/ethyl acetate (0.65g), m.p. 164°C.

Found: C, 59.76; H, 7.22; N, 3.72%
($C_{17}H_{25}NO_3.C_2H_2O_4$) requires: C, 59.83; H, 7.14; N, 3.67%

Example 29

4-[2-(4-Fluorophenoxy)ethyl]-1-propylpiperidine oxalate

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-propylpiperidine (1.85g), 4-fluorophenol (1.12g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with oxalic acid gave a white solid which was recrystallised from methanol/ethyl acetate (0.3g), m.p. 109-112°C.

Found: C, 59.66; H, 7.46; N, 3.80%
($C_{16}H_{24}FNO.C_2H_2O_4.0.5H_2O$) requires: C, 59.50; H, 7.43; N, 3.86%

Example 30

4-[2-(4-Fluorophenoxy)ethyl]-1-(3-phenylpropyl)piperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-(3-phenylpropyl)piperidine (2.47g), 4-fluorophenol (1.12g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from methanol/ethyl acetate (0.65g), m.p. 111-113°C.

Found: C, 68.04; H, 7.72; N, 3.83; Cl, 9.11%
($C_{22}H_{28}FNO.HCl.0.5H_2O$) requires: C, 68.23; H, 7.75; N, 3.60; Cl, 9.04%

Example 31

4-[2-(4-Fluorophenoxy)ethyl]-1-heptylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-heptylpiperidine (2.27g), 4-fluorophenol (1.12g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid

which was recrystallised from methanol/ethyl acetate (1.1g), m.p. 139-141°C.

Found: C, 66.71; H, 9.32; N, 4.05; Cl, 10.08%
($C_{20}H_{32}FNO.HCl$) requires: C, 67.10; H, 9.29; N, 3.91; Cl, 9.90%

Example 32

4-[2-(3,4-Methylenedioxyphenoxy)ethyl]-1-heptylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-heptylpiperidine (2.27g), sesamol (1.38g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from methanol/ethyl acetate (0.65g), m.p. 129-231°C.

Found: C, 65.61; H, 8.85; N, 3.71; Cl, 9.26%
($C_{21}H_{33}NO_3.HCl$) requires: C, 65.69; H, 8.93; N, 3.65; Cl, 9.23%

Example 33

4-[2-(4-Fluorophenoxy)ethyl]-1-(2-ethyl)butylpiperidine oxalate

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-(2-ethyl)butylpiperidine (2.97g), 4-fluorophenol (1.08g),

triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with oxalic acid gave a white solid which was recrystallised from methanol/ethyl acetate (0.65g), m.p. 137-138°C.

Found: C, 63.24; H, 8.26; N, 3.58%
($C_{19}H_{30}FNO.C_2H_2O_4$) requires: C, 63.46; H, 8.11; N, 3.52%

Example 34

4-[2-(3,4-Methylenedioxyphenoxy)ethyl]-1-(2-ethyl)butylpiperidine oxalate

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-(2-ethyl)butylpiperidine (2.25g), sesamol (1.32g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with oxalic acid gave a white solid which was recrystallised from methanol/ethyl acetate (1.25g), m.p. 133-134°C.

Found: C, 62.05; H, 7.88; N, 3.39%
($C_{20}H_{31}NO_3.C_2H_2O_4$) requires: C, 62.39; H, 7.85; N, 3.31%

Example 35

1-Cyclohexylmethyl-4-[2-(3,4-methylenedioxyphenoxy)ethyl]piperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 1-cyclohexylmethyl-4-(2-hydroxyethyl)piperidine (2.25g), sesamol (1.38g),

triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from methanol/ethyl acetate (1.72g), m.p. 177-178°C.

Found: C, 66.01; H, 8.44; N, 3.85; Cl, 9.39%
($C_{21}H_{31}NO_3$.HCl) requires: C, 66.04; H, 8.44; N, 3.67; Cl, 9.28%

Example 36

4-[2-(4-Fluorophenoxy)ethyl]-1-cyclohexylmethylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 1-cyclohexylmethyl-4-(2-hydroxyethyl)piperidine (2.25g), 4-fluorophenol (1.08g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from methanol/ethyl acetate (0.98g), m.p. 178 - 180°C.

Found: C, 67.68; H, 8.85; N, 4.12; Cl, 9.87%
($C_{20}H_{30}FNO$.HCl) requires: C, 67.68; H, 8.78; N, 3.94; Cl, 9.96%

Example 37

1-(3-Methylbutyl)-4-[2-(3,4-methylene-dioxyphenoxy)ethyl]piperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 1-(3-methylbutyl)-4-(2-hydroxyethyl)-piperidine (2.0g), sesamol (1.38g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from methanol/ethyl acetate (0.17g), m.p. 168-169°C.

Found: C, 63.95; H, 8.50; N, 4.05; Cl, 10.17%
($C_{19}H_{29}NO_3$.HCl) requires: C, 64.12; H, 8.50; N, 3.94; Cl, 9.96%

Example 38

1-Benzyl-4-[2-(4-fluorophenoxy)ethyl]-1-piperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 1-benzyl-4-(2-hydroxyethyl)piperidine (3.83g), 4-fluorophenol (1.96g), triphenylphosphine (4.61g) and diethyl azodicarboxylate (2.78g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from methanol/ethyl acetate (2.42g), m.p. 175 -176°C.

Found: C, 68.48; H, 7.22; N, 3.92; Cl, 10.07%
($C_{20}H_{25}FNO$.HCl) requires: C, 68.66; H, 7.20; N, 4.00; Cl, 10.13%

Example 39

4-[2-(4-Fluorophenoxy)ethyl]-1-(2-phenylethyl)-piperidine hydrochloride

A mixture of 4-[2-(4-fluorophenoxy)ethyl]-piperidine hydrochloride (0.57g) and sodium hydride (80% in oil) (0.146g) in dimethylformamide (10ml) was stirred under nitrogen until effervesence had subsided. 2-Phenylethyl bromide (0.3ml) was added and the mixture stirred for 48 hours. The mixture was poured into water (50ml) and extracted with ether. The ether phase was washed with dilute hydrochloric acid and the resulting precipitate collected by filtration. Recrystallisation from water gave the title compound (0.228g) m.p. 210-212°C

Found: C, 69.61; H, 7.48; N, 3.96; Cl, 9.77%
($C_{21}H_{26}FNO.HCl$) requires: C, 69.12; H, 7.73; N, 3.84; Cl, 9.72%

Example 40

4-[2-(4-Fluorophenoxy)ethyl]-1-(4-phenylbutyl)-piperidine hydrochloride

The title compound was prepared in a similar manner to example 39 starting from 4-[2-(4-fluorophenoxy)ethyl]-piperidine hydrochloride (1.0g), sodium hydride (80% in oil) (0.3g) and 4-phenylbutyl chloride (0.649g) in dimethylformamide (20ml) and recrystallising the product from ethyl acetate/methanol, yield (0.39g), m.p. 166-168°C.

Found: C, 70.20; H, 8.00; N, 3.87; Cl, 8.91%
($C_{23}H_{30}FNO.HCl$) requires: C, 70.48; H, 7.97; N, 3.57; Cl, 9.05%

Example 41

1-(3,3-Diphenylpropyl)-4-[2-(4-fluorophenoxy)ethyl]-piperidine oxalate

A mixture of 4-[2-(4-fluorophenoxy)ethyl]-piperidine hydrochloride (2.0g), 3,3-diphenylpropane-1-ylmethanesulphonate (2.23g) and sodium hydride (80% in oil) (0.58g) in dimethylformamide (40ml) was stirred at 60°C under nitrogen for 48 hours. The mixture was poured into water (200ml) and extracted with ether. The ether phase was treated with dilute hydrochloric acid and an oil precipitated. The oil was separated and dissolved in dichloromethane. The dichloromethane solution was washed with dilute sodium hydroxide solution, dried over sodium sulphate and the solvent removed. The residue was dissolved in ethyl acetate and treated with oxalic acid when the title compound crystallised. Yield (0.963g), m.p. 160-161°C

Found: C, 70.96; H, 6.75; N, 2.83%
($C_{28}H_{32}FNO.C_2H_2O_4$) requires: C, 70.98; H, 6.90; N, 2.66%

Example 42

4-[2-(4-Fluorothiophenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (2.00g), 4-fluorothiophenol (1.28g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from ethyl acetate to give the title compound as white plate crystals (0.33g), m.p.164-165°C.

Found: C, 62.41; H, 8.47; N, 4.09; Cl, 10.17%
($C_{18}H_{28}FNS.HCl$) requires: C, 62.49; H, 8.45; N, 4.05; Cl, 10.25%

Example 43

4-[2-(3,4-Dichlorothiophenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (2.00g), 3,4-dichlorothiophenol (1.79g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from ethyl acetate to give the title compound as a white crystalline solid (0.77g), m.p.158-159°C.

Found: C, 54.41; H, 7.11; N, 3.48; Cl^-, 8.89%
($C_{18}H_{27}Cl_2NS.HCl$) requires: C, 54.48; H, 7.11; N, 3.53; Cl^-, 8.93%

Example 44

1-Pentyl-4-(3-phenylpropyl)piperidine hydrochloride

A mixture of 4-(3-phenylpropyl)piperidine (5g), 1-bromopentane (7.42g), potassium carbonate (10g) and ethanol (125ml) was heated at reflux for 18 hours. The solution was filtered, and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane and the dichloromethane solution washed with dilute sodium hydroxide solution, dried over sodium sulphate and the solvent removed. The residue was treated with hydrogen chloride in ether to give a solid. Recrystallisation from ethyl acetate gave the title compound (4.19g), m.p. 188-189°C.

Found: C, 72.56; H, 10.29; N, 4.58; Cl, 11.44%
($C_{19}H_{31}N.HCl.0.25H_2O$) requires: C, 72.56; H, 10.36; N, 4.45; Cl, 11.27%

Example 45

4-[2-(4-Fluorophenyl)ethyl]-1-pentylpiperidine hydrobromide

A mixture of 4-[2-(4-fluorophenyl)ethyl]-1-pentylpyridinium bromide (3.0g), platinum oxide (0.6g) and ethanol (100ml) was shaken under an atmosphere of hydrogen for 15 minutes. The mixture was filtered and the filtrate was evaporated to dryness. The residue was recrystallised from methanol/ethyl acetate to give the title compound. m.p. 173-174°C.

Example 46

4-[2-(4-Nitrophenoxy)ethyl]-1-pentylpiperidine hydrochloride

A mixture of 4-(2-hydroxyethyl)-1-pentylpiperidine (2.5g), sodium hydride (60% in oil) (0.42g) and dimethylformamide (20ml) was heated at 50°C for 1.5 hours. 1-Fluoro-4-nitrobenzene (2.14ml) was added and the mixture was stirred at 50° for 5 hours. The mixture was cooled, poured into water and extracted with dichloromethane. The dichloromethane extracts were dried over magnesium sulphate and the solvent removed. The residue was chromatographed on silica gel, with methanol/dichloromethane as eluent, and the product was treated with hydrogen chloride to give a yellow solid which was recrystallised from ethyl acetate to give the title compound as a yellow crystalline solid (0.937g), m.p.174-176°C.

Found: C, 60.35; H, 8.15; N, 7.85; Cl^-, 9.70% ($C_{18}H_{28}NO_3.HCl$) requires: C, 60.58; H, 8.19; N, 7.85; Cl, 9.93%

Example 47

4-[2-(2-Fluorophenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (1.5g), 2-fluorophenol (0.84g), triphenylphosphine (1.96g) and diethyl azodicarboxylate (1.19ml). Treating the product with hydrogen chloride gave a white solid which

was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (0.87g), m.p.150-152°C.

Found: C, 65.14; H, 8.87; N, 4.30; Cl^-, 10.82% ($C_{18}H_{28}FNO.HCl$) requires: C, 65.54; H, 8.86; N, 4.25; Cl, 10.75%

Example 48

4-[2-(4-tert-Butylphenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (1.5g), 4-tert-butylphenol (1.127g), triphenylphosphine (1.96g) and diethyl azodicarboxylate (1.19g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (1.23g), m.p.189-191°C.

Found: C, 71.67; H, 10.50; N, 3.88; Cl^-, 9.68% ($C_{22}H_{37}NO.HCl$) requires: C, 71.8; H, 10.41; N, 3.81; Cl, 9.63%

Example 49

1-Pentyl-4-[2-(4-trifluoromethoxyphenoxy)ethyl]piperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine

(1.5g), 4-trifluoromethoxyphenol (1.335g), triphenylphosphine (1.96g) and diethyl azodicarboxylate (1.19ml). Treating the product with hydrogen chloride gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (0.95g), m.p.154-156°C.

Found: C, 57.29; H, 7.31; N, 3.52; Cl^-, 8.59%
($C_{19}H_{28}F_3NO_2$.HCl) requires: C, 57.64; H, 7.38; N, 3.54; Cl, 8.96%

Example 50

4-[2-(4-iso-Propylphenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (1.5g), 4-isopropylphenol (1.02g), triphenylphosphine (1.96g) and diethyl azodicarboxylate (1.19ml). Treating the product with hydrogen chloride gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (1.21g), m.p.185-187°C.

Found: C, 71.35; H, 10.23; N, 4.05; Cl^-, 10.08%
($C_{21}H_{35}NO$.HCl) requires: C, 71.26; H, 10.25; N, 3.96; Cl, 10.02%

Example 51

4-[2-(3-iso-Propylphenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (1.5g), 3-isopropylphenol (1.02g), triphenylphosphine (1.96g) and diethyl azodicarboxylate (1.19ml). Treating the product with hydrogen chloride gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (0.5g), m.p.166-168°C.

Found: C, 71.40; H, 10.30; N, 3.97; Cl^-, 10.00%
($C_{21}H_{35}NO.HCl$) requires: C, 71.26; H, 10.25; N, 3.96; Cl, 10.02%

Example 52

4-[2-(3-tert-Butylphenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (1.5g), 3-tert-butylphenol (1.127g), triphenylphosphine (1.96g) and diethyl azodicarboxylate (1.19g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (0.80g), m.p.171-173°C.

Found: C, 71.80; H, 10.57; N, 3.88; Cl^-, 9.67%

($C_{22}H_{37}NO.HCl$) requires: C, 71.8; H, 10.41; N, 3.81; Cl, 9.63%

Example 53

4-[2-(2-phenylphenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (1.5g), 2-phenylphenol (1.28g), triphenylphosphine (1.96g) and diethyl azodicarboxylate (1.19g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (1.05g), m.p.175-177°C.

Example 54

1-Pentyl-4-[2-(4-trifluoromethylphenoxy)ethyl]-piperidine oxalate

A mixture of 4-(2-hydroxyethyl)-1-pentylpiperidine (2.0g), sodium hydride (60% in oil) (0.4g) and dimethylformamide (20ml) was refluxed 1.5 hours. 4-Fluoro-trifluoromethylbenzene (1.64ml) was added and the mixture was refluxed for 18 hours. The mixture was cooled, poured into water and extracted with ether. The ether extracts were dried over magnesium sulphate and the solvent was removed. The residue was chromatographed on silica gel with methanol/dichloromethane as eluent and the product was treated with oxalic acid to give solid. This was

recrystallised from ethyl acetate/methanol to give the title compound. (0.5g), m.p.101-103°C.

Found: C, 57.76; H, 7.00; N, 3.27%
($C_{19}H_{28}F_3NO.C_2H_2O_4.0.1\ H_2O$) requires: C, 57.9; H, 6.9; N, 3.2%

Example 55

4-[2-(3,5 Dichlorophenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (2.0g), 3,5-dichlorophenol (1.63g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (1.1g), m.p.168-170°C.

Found: C, 56.80; H, 7.40; N, 3.64; Cl^-, 9.33; Cl, 27.92%
($C_{18}H_{27}Cl_2NO.HCl$) requires: C, 56.78; H, 7.41; N, 3.68; Cl^-, 9.30; Cl, 27.93%

Example 56

4-[2-(3,4-Dichlorophenoxy)ethyl]-1-heptylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-heptylpiperidine (2.27g), 3,4 dichlorophenol (1.63g), triphenylphosphine

(2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (0.7g), m.p.138-139°C.

Found: C, 58.87; H, 7.88; N, 3.50; Cl^-, 8.68; Cl, 26.00% ($C_{20}H_{31}Cl_2NO.HCl$) requires: C, 58.76; H, 7.89; N, 3.43; Cl^-, 8.68; Cl, 26,01%

Example 57

4-[2-(3,4-Dichlorophenoxy)ethyl]-1-(3-phenylpropyl)piperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-(3-phenylpropyl)-piperidine (2.47g), 3,4-dichlorophenol (1.63g), triphenylphosphine (2.62g) and diethyl azodicarboxylate (1.74g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (0.75g), m.p.137-138°C.

Found: C, 61.24; H, 6.45; N, 3.36; Cl^-, 8.7% ($C_{22}H_{27}Cl_2NO.HCl.0.1\ H_2O$) requires: C, 61.56; H, 6.34; N, 3.27; Cl, 8.30%

Example 58

1-Cyclopropylmethyl-4-[2-(4-fluorophenoxy)ethyl]-piperidine oxalate

The title compound was prepared in a similar manner to example 41 from 4-[2-(4-fluorophenoxy)ethyl]-piperidine hydrochloride (2.0g), bromomethylcyclopropane (2.0ml) and sodium hydride (80% in oil) (0.58g) in dimethylformamide (40ml). Treating the product with oxalic acid in ethyl acetate gave a solid which was recrystallised from ethyl acetate to give the title compound. Yield, (0.963g) m.p. 129-132°C

Found: C, 61.95; H, 7.05; N, 3.91%
($C_{17}H_{24}FNO.C_2H_2O_4$) requires: C, 62.11; H, 7.13; N, 3.81%

Example 59

1-(3,3-Diphenylprop-2-enyl)-4-[2-(4-fluorophenoxy)ethyl]-piperidine 1-(3,3-Diphenylprop-2-enyl)-4-[2-(4-fluorophenoxy)ethyl]-piperidine oxalate

Methanesulphonyl chloride ((0.46ml) was added to a solution of 1,1-diphenyl-2-hydroxymethylethylene (1.14g) in tetrahydrofuran (20ml). The mixture was stirred for 1 hour when 4-[2-(4-fluorophenoxy)ethyl]-piperidine (1.42g) and triethylamine (0.8ml) was added. The mixture was stirred under nitrogen for 48 hours then heated at reflux for 8 hours. The mixture was poured into water (200ml) and extracted with ether. The ether phase was dried over

magnesium sulphate, filtered and the solvent removed. The residue was chromatographed on silica gel with methanol/dichloromethane as eluent and the product was treated with oxalic acid to give solid. This was recrystallised from ethyl acetate/methanol to give the title compound. (0.687g), m.p.174-176°C.

Found: C, 70.84; H, 6.34; N, 2.93%
($C_{28}H_{30}FNO.C_2H_2O_4$) requires: C, 71.27; H, 6.38; N, 2.77%

Example 60

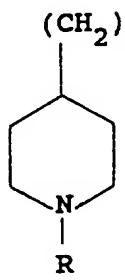
4-[2-(2-Benzylphenoxy)ethyl]-1-pentylpiperidine hydrochloride

The title compound was prepared in a similar manner to example 1 from 4-(2-hydroxyethyl)-1-pentylpiperidine (1.5g), 2-hydroxydiphenyl methane (1.38g), triphenylphosphine (1.96g) and diethyl azodicarboxylate (1.19g). Treating the product with hydrogen chloride gave a white solid which was recrystallised from ethyl acetate/methanol to give the title compound as a white crystalline solid (1.65g), m.p.119-120°C.

Found: C, 73.32; H, 8.94; N, 3.61; Cl, 8.70%
($C_{25}H_{35}NO.HCl.0.3H_2O$) requires: C, 73.59; H, 8.89; N, 3.43; Cl, 8.69%

Claims:

1. A compound of structure (I):



(I)

in which
R is C_{1-8}alkyl(phenyl)p, C_{2-8}alkenyl(phenyl)p, C_{2-8}alkenyl(phenyl)p, C_{3-8}cycloalkyl or C_{1-8}alkylC_{3-8}cycloalkyl;
p is 0 to 2;
n is 0 to 6;
A is a bond, oxygen, sulphur or NR^1;
R^1 is hydrogen, C_{1-8}alkyl or phenylC_{1-4}alkyl;
m is 0 to 3; and
Ar is aryl or heteroaryl, each of which may be optionally substituted,
or a salt thereof.

2. A compound according to claim 1 wherein R is C_{1-8} alkyl, phenyl(C_{1-8})alkyl or phenyl(C_{2-8})-alkenyl.

3. A compound according to claim 1 or claim 2 in which A is oxygen.

4. A compound according to any of claims 1 to 3 wherein n is 0 to 3.

5. A compound according to any claims 1 to 4 wherein m is 0 to 3.

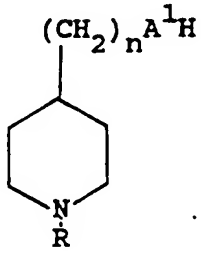
6. A compound according to any of claims 1 to 5 in which Ar is optionally substituted phenyl.

7. A compound according to claim 1 which is:
4-[2-(4-trifluoromethylphenoxy)ethyl]-1-pentylpiperidine,
4-[2-(3-trifluoromethylphenoxy)ethyl]-1-pentylpiperidine,
4-[2-(4-fluorophenoxy)ethyl]-1-pentylpiperidine,
4-[2-(3,4-methylenedioxyphenoxy)ethyl]-1-pentylpiperidine,
4-(2-phenoxyethyl)-1-pentylpiperidine,
4-[2-(4-phenylphenoxy)ethyl]-1-pentylpiperidine,
4-[2-(4-benzyloxyphenoxy)ethyl]-1-pentylpiperidine,
4-[2-(4-fluorophenoxy)ethyl]-1-cinnamylpiperidine,
4-(4-fluorobenzyloxy)-1-pentylpiperidine,
4-[2-(3,4-dichlorophenoxy)ethyl]-1-pentylpiperidine,
4-[2-(4-benzylphenoxy)ethyl]-1-pentylpiperidine,
4-[2-(3,4-dichlorophenoxy)ethyl]-1-cinnamylpiperidine,
4-[2-(4-fluorophenoxy)ethyl]-1-(3-phenylpropylpiperidine,
4-[2-(4-fluorophenoxy)ethyl]-1-heptylpiperidine,
1-(3,3-diphenylpropyl)-4-[2-(4-fluorophenoxy)ethyl]-piperidine,
4-[2-(3,4-dichlorothiophenoxy)ethyl]-1-pentylpiperidine,
4-[2-(4-tert-butylphenoxy)ethyl]-1-pentylpiperidine,
4-[2-(4-iso-propylphenoxy)ethyl]-1-pentylpiperidine,
4-[2-(3,4-dichlorophenoxy)ethyl]-1-(3-phenylpropyl)-piperidine, or
1-cyclopropylmethyl-4-[2-(4-fluorophenoxy)ethyl]-piperidine;

or a pharmaceutically acceptable salt thereof.

8. A process for preparing a compound of structure (I) which comprises:

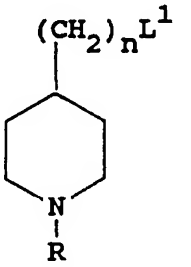
(a) for compounds of structure (I) in which A is O, S or NR^1, reaction of a compound of structure (II):



(II)

in which R and n are as described for structure (I) and A^1 is O, S or NR^1, with a compound of structure $L(CH_2)_mAr$ in which m and Ar are as described for structure (I), and L is a leaving group;

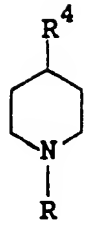
(b) for compounds of structure (I) in which A is O, S or NR^1, reaction of a compound of structure (III):



(III)

in which n and R are as described for structure (I) and L^1 is a group displaceable by a nucleophile, with a compound of structure $HA^1(CH_2)_mAr$ where m and Ar are as described for structure (I) and A^1 is as described for structure (II); or

(c) for compounds of structure (I) in which A is NR^1, reduction of a compound of structure (IV) :



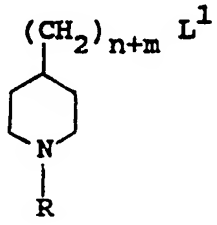
(IV)

in which R^4 represents the group

$-(CH_2)_nN(R^1)\overset{O}{\overset{\|}{C}}(CH_2)_{m-1}Ar$ or $-(CH_2)_{n-1}\overset{O}{\overset{\|}{C}}N(R^1)(CH_2)_mAr$,

and n, m, R and Ar are as described for structure (I);

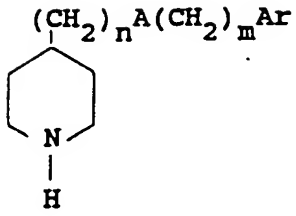
(d) for compounds of structure (I) in which A is a bond, reaction of a compound of structure (V) :



(V)

(wherein R, L^1, n and m are as hereinbefore defined) with a compound of structure X^1Ar in which Ar is as described for structure (I), and X^1 is an alkali metal;

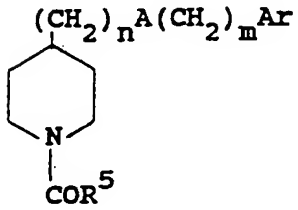
(e) introduction of the group R into a compound of formula (VI) :



(VI)

by reaction with a compound RL^2, wherein L^2 is a leaving group;

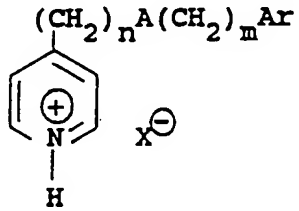
(f) Reduction of a compound of formula (VII) :



(VII)

wherein R^5 is C_{1-7}alkyl(phenyl)p, C_{2-7}alkenyl(phenyl)p, C_{2-7}alkynyl(phenyl)p or C_{1-7}alkylC_{3-8}cycloalkyl;

(g) Reduction of a compound of structure (VIII):



(VIII)

wherein R, A, Ar m and n are as hereinbefore defined and X^- is a counter ion;
and optionally thereafter forming a salt.

9. A pharmaceutical composition comprising a compound of structure (I) as claimed in any of claims 1 to 7 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier.

10. A compound of structure (I) according to any of claims 1 to 7 or a pharmaceutically acceptable salt thereof for use in therapy.

11. Use of a compound of structure (I) as defined in any of claims 1 to 7, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition caused or exacerbated by the accumulation of calcium in the brain cells of mammals.

12. Method of treating a condition caused or exacerbated by the accumulation of calcium in the brain cells of mammals which comprises administering to a subject in need thereof an effective amount of a compound of structure (I) as defined in any of claims 1 to 7 or a pharmaceutically acceptable salt thereof.

13. Method according to claim 12 wherein the condition is stroke.

14. Method according to claim 12 or claim 13 wherein the mammal is a human.

INTERNATIONAL SEARCH REPORT

International Applic. ..n No PCT/GB 91/01340

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 211/22 C 07 D 211/14 C 07 D 211/46
C 07 D 401/12 A 61 K 31/445

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 211/00 C 07 D 401/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	EP,A,0181618 (BASF) 21 May 1986, see example 10 ---	1,2,4-6
X	J. Chem. Soc. B, 1971, P. Scheiber et al.: "Chemistry of tropan-3-yl ethers. Part I. Synthesis of tropan-3-yl ethers", pages 2145-2149, see table 3, N-methyl-4-phenoxy-piperidine ---	1-6
X	Chemical Abstracts, vol. 95, 1981, (Columbus, Ohio, US), C.E. Berkoff et al.: "The reductive decyanation of nitriles by alkali fusion", see page 667, abstract 24742f, & Synth. Commun. 1980, 10(12), 939-45 ---	1,2,4-6
X	Chemical Abstracts, vol. 87, 1977, (Columbus, Ohio, US), see page 629, abstract 102382q, & US, A, 4031221 (AMERICAN HOECHST CORP.) 21 June 1977 --- -/-	1-6,9-11

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
04-10-1991	20. 11. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme. M. van der Drift

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	Archiv Pharmazie, vol. 312, August 1979, Verlag Chemie, (Weinheim, DE), K. Rehse et al.: "Neuropsychotrope Aktivität dopaminanaloger Piperidin- und Piperazinderivate", pages 670-681, see the whole article; page 674, compound 5	1,2,4-6 ,9-11
X	EP,A,0372776 (PFIZER) 13 June 1990, see page 4, lines 19-28; claims 1,10	1,2,4-6 ,9-11
X	EP,A,0077427 (SYNTHELABO) 27 April 1983, see the whole document; examples 12,15,17,20-23,26,27,29,33,42,43,45; page 13, lines 6-8	1-6,9-11
X	EP,A,0229391 (EISAI) 22 July 1987, see compound 15; page 15, lines 7-21	1-6,9-11
X	EP,A,0320032 (JANSSEN) 14 June 1989, see example 12a	1-6,9-10

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

see sheet -B-

2. ☐ Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA 210 (suppl. Sheet (2)

Subject matter excluded from patentability:

Claims 12-14: Treatment of the human body (rule 39.IV PCT)

Obscurity:

"Thiophenoxy" in claim 7 and dependent claims

Although it might be inferred from the context that the applicant claims "thienyl-oxy-" derivatives the ambiguity remains and thienyl derivatives have not been searched.

Lack of conciseness:

"AR is aryl or heteroaryl, each of which may be optionally substituted" (Claim 1 and dependent claims)

Claims 1-6 and 8-11 do only comply with the requirements of art. 6 PCT as far as "A" is oxygen.
Furthermore, the number of conceivable structures resulting from all claimed combinations of "n", "m" and "A" (claiming even simple 4-aryl-subst. piperidines where N = O, M = O and A = bond) precludes a comprehensive and economically justified search.

Hence only 4-subst.-oxyethyl-N-hydrocarbyl-piperidines have been searched comprehensively.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9101340 SA 50353

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 25/10/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0181618	21-05-86	DE-A-	3441929	28-05-86
		CA-A-	1264752	23-01-90
		JP-A-	61122268	10-06-86
		US-A-	4656282	07-04-87
EP-A- 0372776	13-06-90	WO-A-	9006303	14-06-90
		CA-A-	2004249	02-06-90
EP-A- 0077427	27-04-83	None		
EP-A- 0229391	22-07-87	AU-A-	6690686	02-07-87
		JP-A-	62234065	14-10-87
		US-A-	4942169	17-07-90
		US-A-	5039681	13-08-91
		US-A-	4849431	18-07-89
EP-A- 0320032	14-06-89	AU-A-	2575188	25-05-89
		JP-A-	1207278	21-08-89
		US-A-	4992433	12-02-91